

28. (Amended) A method for inhibiting unwanted activation of a *hedgehog-patched* pathway in an animal, comprising topically administering to the animal a composition comprising a purified hedgehog antagonist, or prodrug form thereof which is converted to a hedgehog antagonist under physiological conditions of the host animal, in a sufficient amount to reduce the unwanted activation of the *hedgehog-patched* pathway in a cell of the animal, wherein the hedgehog antagonist is an organic molecule which interacts with *smoothened* ~~or a complex comprising *smoothened*~~ and lessens the severity of a *hedgehog* gain-of-function, *patched* loss-of-function, or *smoothened* gain-of-function phenotype.

36. A method for inhibiting unwanted activation of a *hedgehog-patched* pathway in an animal, comprising  
providing a cell,  
treating the cell with a test compound, wherein the test compound is an organic molecule having a molecular weight less than 750 amu,  
detecting a decrease in the level of activation of a *hedgehog-patched* pathway in the cell indicative of a *hedgehog* inhibitory activity of the test compound, and  
administering to the animal a composition comprising the test compound having a *hedgehog* inhibitory activity in an amount sufficient to reduce the activation of a *hedgehog-patched* pathway in a cell of the patient.

#### **REMARKS**

Following entry of the foregoing amendments, claims 1, 15-17, 20-23, 27, 28, and 36 constitute the pending claims in the present application. Applicants have amended claims 15-17 to remove dependency to a non elected claim, in accordance with the previous restriction requirement. Applicants have amended claim 1 by changing the term “binding to” to “interacting with”. (See Specification on page lines 10-17; See also, Exhibit A) Applicants have amended claims 15-17 to remove dependency to a non-elected claim in accordance to the previous restriction requirement. Applicants have amended claim 22 by removing the redundant term “[applied]”. Applicants have amended claim 28 by removing the phrase “a complex comprising *smoothened*”. (See Specification on page lines 10-17; See also Exhibit A) Amendments presented in this response are made solely to expedite prosecution of the claims in

the present application. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action. Applicants respectfully request reconsideration in view of the following remarks.

1. Applicants note the Examiner's remarks acknowledging Applicants' election with traverse of Group 2 in Paper No. 15. Applicants additionally note that Applicants' traversal grounds with respect to simultaneous examination of Groups 1-16 have not been found persuasive and the requirement has been made FINAL.

2. Applicants note that based on Applicants' election, claims 1, 15-17, 20-23, 27, 28, and 36 will be examined to the extent that they read on compounds having the basic chemical structure of cyclopamine and jervine.

3-4. Claims 1, 15-17, 20-23, 27, 28, and 36 are rejected under 35 U.S.C. 112, first paragraph, because the present specification is alleged to not reasonably provide enablement for all organic molecules having a molecular weight less than 750 amu. The Office Action stated that "[T]he present specification ... does not provide guidance as to how the ordinary artisan in the art would make and/or use other molecules or hedgehog antagonist commensurate in the scope with the claimed invention." Claims 1, 27, and 36 are the independent claims containing molecular weight limitations. Claims 15-17 and 20-23 are dependent on claim 1, and thus are not separately discussed below. Applicants submit that the rejection is moot with respect to claim 28, because the claim does not have a molecular weight limitation. Applicants respectfully traverse the rejection with respect to the remaining claims 1, 27, and 36.

Applicants assert that the present specification, coupled with information known in the art at the time of filing, sufficiently enabled the skilled artisan to make and use the invention commensurate in scope with the claims 1, 27, and 36. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. (See MPEP 2164.1 quoting *United States v. Teletronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988)) Since the present claims are method claims directed to the use of compounds, the specification need only enable the skilled artisan to use of the type of compounds claimed in the manner claimed. Thus, with respect to the rejection, the skilled artisan needs enabling knowledge on how to select a composition comprising an organic compound with a molecular

weight less than 750 amu, wherein the organic molecule interacts with *smoothened* and lessens the severity of a *hedgehog* gain-of-function, *patched* loss-of-function, or *smoothened* gain-of-function phenotype. Applicants submit that the specification provides sufficient guidance on how to identify a compound which interacts with *smoothened* and lessens the severity of a *hedgehog* gain-of-function, *patched* loss-of-function, or *smoothened* gain-of-function phenotype. (See Specification on page 78, line 15, to page 80, line 5 for screening assays; *See also*, Specification on page 80, line 15, for examples of disruption of hedgehog signaling using steroid alkaloids.) Applicants further submit that it is generally known to a skilled artisan how to determine whether a compound has a molecular weight less than 750 amu, e.g., through use of spectrometry or, where the structure is known, by calculating it from the average atomic weights of the constituent atoms. Therefore, Applicants assert that the present specification, coupled with knowledge generally available at the time of filing, disclosed sufficient information to enable the skilled artisan to practice the invention without undue experimentation. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

5-6. Claims 1, 15-17, 20-23, 27, 28, and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Applicants respectfully traverse the rejection.

(i) The Office Action stated the phrases (a) “inhibiting unwanted activation of a hedgehog-patched pathway” and (b) “a purified organic molecule having a molecular weight less than 750 amu” create confusion as to the metes and bounds of the invention because “it is unclear what other compounds are encompassed by the instant claims”. With respect to (a), Applicants submit that the dictionary meaning of the term “unwanted” is clear: (1) : not wanted ; (2) : not needed or useful : superfluous, unnecessary, or (3) : detrimental in character : faulty, undesirable (See Webster's Third New International Dictionary, Unabridged, 1996). In the clinical setting, the phrase unwanted activation of hedgehog signaling, in accordance with the plain meaning of the term, includes signaling that is not wanted not needed or useful : superfluous, unnecessary detrimental in character : faulty, undesirable. Specific manifestations of unwanted activation of hedgehog-patched signaling include unwanted hair growth, and uncontrolled cell proliferation. (See Specification on pages 60-64 for these and other examples of unwanted activation of hedgehog-patched signaling.) The compounds claimed in the instant method claims inhibit such unwanted activation. Thus, Applicants assert that the skilled artisan

would not be confused as to the metes and bounds of the term “unwanted activation of a hedgehog-patched pathway”.

With respect to (b), Applicants submit that the phrase does not stand in isolation, but rather refers to a compound which interacts with *smoothened* and lessens the severity of a *hedgehog* gain-of-function, *patched* loss-of-function, or *smoothened* gain-of-function phenotype. Applicants submit that the specification provides sufficient disclosure on how to identify a compound which interacts with *smoothened* and lessens the severity of a *hedgehog* gain-of-function, *patched* loss-of-function, or *smoothened* gain-of-function phenotype. (See Specification on page 78, line 15- page 80, line 5 for screening assays; *See also*, Specification on page 80, line 15 for examples of disruption of hedgehog signaling using steroid alkaloids.) Thus, Applicants submit that the skilled artisan would not have been confused by the use of the terms “inhibiting unwanted activation of a hedgehog-patched pathway”, and (b) “a purified organic molecule having a molecular weight less than 750 amu”.

Applicants further assert that with respect to the phrase “a purified organic molecule having a molecular weight less than 750 amu”, the scope of the disclosure is commensurate with the scope of the claim. With regards to the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. (See MPEP 2164.08 quoting *In re Moore*, 439 F.2d 1232, 1236, 169 USPQ 236, 239 (CCPA 1971)) The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of the enablement involves two stages of inquiry. The first is to determine how broad the claim is with respect to the disclosure. The entire claim must be considered. The second inquiry is to determine if one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation. (See MPEP 2164.08) As to the first stage of the inquiry, Applicants submit that the breadth of the claim is commensurate with the disclosure provided in the specification. Applicants have disclosed numerous organic molecules that are within the scope of the claim language “a purified organic molecule having a molecular weight less than 750 amu”, and also meet the rest of the limitations in the claims, i.e., lessening the severity of a *hedgehog* gain-of-function, *patched* loss-of-function, or *smoothened* gain-of-function phenotype. Cited compounds include naturally occurring veratrum alkaloids including veratramine, zygacine, solanadine, tomatidine, cyclopamine, cycloposine, jervine, and

muldamine. (See Specification starting on page 31 line 30 to page 42 line 5) As to the second stage of the inquiry, Applicants have disclosed combinatorial libraries of hedgehog antagonists. These libraries may be prepared in the manner described in the specification. Applicants further disclose methods for screening such libraries. (See Specification on page 76 line 25 to page 80 line 5) Thus, Applicants submit that one skilled in the art would have been able to make and use the entire scope of the claimed invention, e.g., preparing, identifying and screening organic molecules with molecular weights of less than 750 amu exhibiting the claimed biological activity, without undue experimentation.

In view of the arguments presented above, Applicants respectfully request reconsideration and withdrawal of the rejections.

(ii) The Office Action stated that claims 15-17 are dependent on cancelled claim 3, and, thus the scope of the invention is unclear. Applicants have amended claims 15-17 to remove dependency on claim 3. Accordingly, Applicants respectfully request removal of the objection.

(iii) The Office Action stated the phrase “prodrug form thereof” in claim 28 is unclear. Applicants have provided a definition for the term “prodrug” in the specification. (See Specification on page 20, ln 21-25) Information which is well known in the art need not be described in detail in the specification. (MPEP 2163) Moieties that could be attached to a therapeutic agent to achieve tissue targeting or enhanced bioavailability have been well known in the art. (See, e.g., Exhibit A) Thus, Applicants submit that the skilled artisan would not have been confused by the use of the term “prodrug” in conjunction with the inhibitors in the present claims. Accordingly, Applicants respectfully request removal of the objection.

7-8. Claims 1, 15-17, 20-23, 27, 28, and 36 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-8, 11-17, 20 and 22 of copending Application No. 09/708,974. Applicants will address this issue when the rejection is no longer merely provisional.

9. Claims 1, 15-17, 20-23, 27, 28, and 36 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-8, 11-31, 43 and 44 of copending Application No. 09/090,622. The co-pending application has now issued as U.S. Patent No. 6,432,970. Applicants will submit a terminal disclaimer if necessary upon indication of allowable subject matter.

10. Claims 1, 15-17, 20-23, 27, 28, and 36 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent 6,288,048. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

11-12. Claims 1, 20, 21, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Gerashchenko et al. The Office Action stated that “Gerashchenko et al. teach the compound jervine and its anti-inflammatory activity...[T]he method of use taught by the reference is encompassed by the instant claims.” Applicants respectfully traverse this rejection.

Gerashchenko et al. do not teach or suggest every element of the present claims, and therefore do not anticipate the claims. To anticipate a claim the reference must teach every element of the claim. (See MPEP 2131) Both claim 1 (claims 20 and 21 are dependent on claim 1) and 36 are method claims directed to inhibiting “unwanted activation of hedgehog-patched pathway”. While Gerashchenko et al. teach the use of jervine for anti-inflammatory purposes, the reference does not teach a method for inhibiting unwanted activation of the hedgehog-patched pathway. Gerashchenko et al. fails to anticipate the present claims because it does not expressly teach every limitation that is present in the pending claims. Thus, Applicants assert that Gerashchenko et al. do not expressly anticipate claim 1 or 36, or claims dependent thereon. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

To the extent that the rejection is maintained under the doctrine of inherency, Applicants still traverse the rejection. As a threshold matter, Gerashchenko et al. use jervine for an indication unrelated to hedgehog-patched signaling. Applicants are unaware of any scientific or patent publication relating activation of hedgehog-patched pathway to inflammation. Furthermore, the fact that the hedgehog-patched pathway may have been inhibited in the experiments described by Gerashchenko et al. is not relevant because, for inherent anticipation of method claims, if a claimed method comprises steps identical to those of a method practiced in the prior art, and the same result would have been achieved in the prior art method, the accidental or unwitting achievement of that result cannot constitute anticipation. *In re Marshall*, 578 F.2d 301, 198 USPQ 344 (CCPA 1978). In *Marshall*, the PTO Board used the *Physician's Desk Reference* (PDR) as a basis for a rejection of the applicant's weight control process. The applicant's process involved anesthetizing certain intestinal nerve ends receptors with oxethazaine. The anesthesia inhibited the release of certain appetite stimulating hormones

thereby inhibiting appetite. The PDR had disclosed that oxethazaine inhibits the release of gastrointestinal hormones, and such inhibition would be useful for treating certain gastrointestinal ailments. In reversing the Board's rejection, the court held that the PDR did not teach the use of the compound as a weight control drug. Addressing the issue of inherency, the court further stated that "[I]f anyone ever lost weight by following the PDR teachings it was an unrecognized accident. An accidental or unwitting duplication of an invention cannot constitute an anticipation." (*id.* 304)

Applicants maintain that *Marshall* is controlling in the instant situation. In *Marshall*, the essential question with regards to inherency was not whether oxethazaine had inhibited the release of intestinal hormones in patients prior to the applicant's weight control process, or whether patients had lost weight when oxethazaine was administered to them as an anesthetic. Rather the question was whether the prior reference taught the reader that weight loss can be achieved by using oxethazaine. Thus, if the reference does not teach or suggest the claimed process, then the claimed process is new and unobvious in view of the reference.

The instant claim is directed to inhibiting unwanted activation of the hedgehog-patched pathway in an animal. Applicants point out that the MPEP does not foreclose patentability where "new and unobvious uses of old structures and compositions" are present (MPEP 2112.02, original emphasis) Under *Marshall*, "accidental or unwitting duplication of an invention cannot constitute an anticipation." (*Marshall*, 578 F.2d at 304) Thus, to sustain anticipation by inherency, Gerashchenko et al. must teach or suggest inhibition of the hedgehog-patched pathway in a manner that is not accidental or unwitting. Gerashchenko et al., however, fails to teach or suggest a method for inhibiting unwanted activation of the hedgehog-patched pathway. Furthermore, one of ordinary skill in the art would not have found another reference which teaches or suggests a connection between inflammation and unwanted activation of the hedgehog pathway. Thus, Applicants assert that Gerashchenko et al. do not inherently anticipate claim 1 or 36, or claims dependent thereon. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

13-14. Claims 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerashchenko et al. In making the rejection, the Office Action stated that Gerashchenko et al. teach the compound jervine and its anti-inflammatory activity; "[T]he instant claims differ from the reference by reciting specific ED<sub>50</sub> values at which signal transduction mediated by the

hedgehog protein is inhibited”; that the reference teaches “decreased granuloma exudates and proliferation as well as adrenal ascorbic acid using 5 mg/kg/day of jervine”; and that determination of concentrations to achieve ED<sub>50</sub> can be made through routine experimentation.

Applicants traverse the rejection

More important than the ED<sub>50</sub> differences between the instant claims and Gerashchenko et al. is the difference arising from the instant claims being drawn to inhibiting unwanted activation of the hedgehog-patched pathway while Gerashchenko et al. do not teach or suggest such inhibition. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (MPEP 2143) Inhibiting unwanted activation of the hedgehog pathway is a limitation of the instant claims. Gerashchenko et al. neither teach nor suggest inhibiting unwanted activation of the hedgehog-patched pathway, whether with jervine or anything else. As far as Applicants are aware, the prior art does not teach or suggest a link between inflammation and unwanted activation of the hedgehog-patched pathway. Thus, one of ordinary skill in the art, having read Gerashchenko et al., would not have had a motivation to use jervine in a manner other than as an anti-inflammatory agent. Furthermore, one of ordinary skill in the art, having read Gerashchenko et al., would not have had the requisite reasonable expectation of success in using jervine as described in the present application, because Gerashchenko et al. do not disclose treatments of animals that have unwanted activation of the hedgehog pathway with jervine. Thus, Applicants assert that the Office Action has not met its burden in establishing a prima facie case of obviousness. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

### **CONCLUSION**

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000. If there are any other fees



due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945**. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

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Respectfully Submitted,



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